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TITLE

Outcome after conservative management or intervention for unruptured brain arteriovenous malformations

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* See SAIVMs collaborators listed at the end of the manuscript

39 **ABSTRACT**

40

41 **Importance** – Whether conservative management is superior to interventional treatment
42 (‘intervention’) for unruptured brain arteriovenous malformations (bAVMs) is uncertain, because
43 of the shortage of long-term comparative data.

44 **Objective** – Long-term comparison of outcomes of conservative management versus intervention
45 for unruptured bAVM.

46 **Design** – Population-based inception cohort study of adults resident in Scotland, first diagnosed
47 with an unruptured bAVM during 1999-2003 or 2006-2010, and followed prospectively using
48 multiple sources to assess handicap and to identify and validate outcome events over 12 years of
49 prospective follow-up.

50 **Exposures** – We compared associations with conservative management (without intervention)
51 versus intervention (endovascular embolization ± neurosurgical excision ± stereotactic
52 radiosurgery).

53 **Main outcomes and measures** – Cox regression analyses, with multivariable adjustment for
54 prognostic factors and baseline imbalances if hazards were proportional, to compare rates of the
55 primary outcome (death or sustained morbidity of any cause, Oxford Handicap Scale score [OHS]
56 ≥2 for at least two successive years [0=no symptoms and 6=death]) and the secondary outcome
57 (non-fatal symptomatic stroke or death due to bAVM, associated arterial aneurysm or
58 intervention).

59 **Results** – Of 204 adults, 101 underwent intervention; they were younger, more likely to have
60 presented with seizure(s), and less likely to have large bAVMs than adults managed conservatively.
61 During a median follow-up of 6·9 years (94% completeness), the rate of progression to the primary
62 outcome was lower with conservative management during the first four years of follow-up [16
63 deaths (4·0 per 100 person-years) and 20 OHS 2-5 (5·5 per 100 person-years) versus 4 deaths (1·0

64 per 100 person-years) and 35 OHS 2-5 (8.8 per 100 person-years), adjusted hazard ratio (HR) 0.59,
65 95% confidence interval (CI) 0.35 to 0.99], but rates were similar thereafter. The rate of the
66 secondary outcome was lower with conservative management during 12 years of follow-up [14
67 events (1.6 per 100 person-years) versus 38 events (3.3 per 100 person-years), adjusted HR 0.37,
68 95% CI 0.19 to 0.72].

69 **Conclusions and relevance** – Among adults diagnosed with unruptured bAVM, the use of
70 conservative management compared with intervention was associated with better clinical
71 outcomes over 4 years. Longer follow-up is required to understand whether this association
72 persists.

73 INTRODUCTION

74

75 Unruptured brain arteriovenous malformations and their associated feeding/nidal arterial
76 aneurysms (collectively termed 'bAVM') have ~1% annual risk of intracranial hemorrhage,^{1,2} which
77 has a one year case fatality of 12%,³ in studies lasting up to ten years.⁴ Interventional treatment
78 ('intervention') by neurosurgical excision, endovascular embolization, or stereotactic radiosurgery
79 can be used alone, or in combination, to attempt to obliterate bAVMs, dependent on their
80 vascular anatomy.⁵ Because interventions may have complications⁶ and the untreated clinical
81 course of unruptured bAVMs can be benign,¹⁻⁴ some patients choose conservative management
82 (without intervention). Unruptured bAVM intervention has been compared with conservative
83 management in a concurrent control group in just one randomized trial (ARUBA
84 [ISRCTN44013133])⁷⁻⁹ and only a few observational studies, all of which have shown harm from
85 intervention in the short-term.^{10,11} Guidelines have endorsed both intervention and conservative
86 management for unruptured bAVMs.^{12,13} Therefore, we began a study in 1999 to assess the long-
87 term outcome for adults affected by bAVM, with or without intervention, in everyday clinical
88 practice.^{14,15}

89

90 METHODS

91

92 The Scottish Intracranial Vascular Malformation (IVM) Study (SIVMS) is a prospective, population-
93 based cohort study that uses anonymized data extracts from the National Health Service Scottish
94 Audit of IVMs (SAIVMs). SAIVMs included adults who were aged ≥16 years and resident in Scotland
95 when first diagnosed with bAVM in 1999-2003 or 2006-2010 (www.saivms.scot.nhs.uk). The audit
96 protocol (www.saivms.scot.nhs.uk/pdf/2008_06_SAIVMs%20protocol_v2.pdf) and research
97 protocol (<http://docdat.ic.nhs.uk>) are published. SAIVMs identified patients through multiple

98 overlapping sources of case ascertainment that included a Scotland-wide collaborative network of
99 neurologists, neurosurgeons, stroke physicians, radiologists, and pathologists and central registers
100 of hospital discharges and death certificates.¹⁵

101

102 **Ethical approval**

103

104 The Multicentre Research Ethics Committee for Scotland (MREC/98/0/48) and the Fife and Forth
105 Valley Research Ethics Committee (08/S0501/76) approved the conduct of observational studies
106 (to which an opt-out consent policy applied) and postal questionnaire studies (which required opt-
107 in consent).

108

109 **Eligibility criteria**

110

111 In this analysis, we included adults in SIVMS with a radiographically- or pathologically-confirmed
112 first-in-a-lifetime definite diagnosis of a bAVM in 1999-2003 or in 2006-2010 inclusive, which was
113 unruptured when diagnosed. The term 'bAVM' included associated nidus/feeding arterial
114 aneurysms, but not intracranial aneurysms remote from the bAVM its arterial supply. We
115 classified adults as receiving intervention if they underwent any of the following treatments for
116 their unruptured bAVM, either alone or in any combination, before the end of follow-up:
117 microsurgical excision, stereotactic radiosurgery, or endovascular (glue or coil) embolization. We
118 classified adults as undergoing 'conservative management' if they did not receive any of these
119 interventions. Decisions about intervention were left to patients and their physicians.

120

121

122

123 **Diagnostic verification**

124

125 Four experienced neuroradiologists verified certainty of bAVM diagnosis on diagnostic brain
126 imaging that had been performed in clinical practice (supported by the Systematic Image Review
127 System tool; <http://www.neuroimage.co.uk/sirsinfo/>). They determined surgical eloquence of
128 nidus location¹⁶ and used catheter angiography to describe vascular anatomy¹⁰ or MRI to measure
129 nidus size.^{17,18}

130

131 **Baseline characteristics**

132

133 We reviewed family (general) practitioner and hospital medical records to establish demographics,
134 medical histories, and the consequences of bAVM presentation on the Oxford Handicap Scale
135 (OHS), which is a derivative of the modified Rankin Scale, ranging from 0 (no symptoms) to 6
136 (death).¹⁹ We reviewed these medical records, brain imaging and reports of pathological
137 examinations to classify the mode of bAVM presentation and clinical outcome events during
138 follow-up. When assessing clinical events at presentation and during follow-up, we also classified
139 whether they were definitely, possibly, or definitely not attributable to the bAVM or an
140 intervention complication. We classified events as possibly attributable to the bAVM when clinical
141 features were anatomically consistent with bAVM location, but another cause (e.g. ischaemic
142 stroke) was possible and neuroradiological investigation had identified neither bAVM hemorrhage
143 nor an alternative cause. We regarded presentations as 'incidental' if the adult had been
144 asymptomatic or if we could not definitely relate their symptoms to the underlying bAVM (e.g.
145 headache); we attributed presentations to epileptic seizure(s) if a seizure was neither
146 symptomatic of a concomitant intracranial hemorrhage nor more likely to be due to another
147 cause.

148

149 **Follow-up**

150

151 The inception point for conservative management was an adult's presentation, which was the date
152 of symptom onset or medical consultation (if asymptomatic) that led to an investigation
153 diagnosing the bAVM. The inception point for intervention was the date of the first intervention
154 for an unruptured bAVM that proceeded after presentation. Follow-up occurred prospectively on
155 an uninterrupted annual basis, using a postal questionnaire to every adult's family practitioner and
156 annual surveillance of family practitioner and hospital medical records, to identify outcome events
157 that had occurred over the preceding year. Consenting participants completed postal
158 questionnaires on each anniversary of bAVM diagnosis, to identify outcome events and assess
159 handicap on the OHS. Two investigators (CPW or RA-SS) independently assessed symptomatic
160 clinical outcome events,¹⁰ using all the contemporaneous clinical, radiographic and pathological
161 records available. In attributing the mode and cause of death we reviewed death certificates,
162 autopsy reports if performed, and clinical records and brain imaging if death occurred in hospital.
163 Extent of bAVM obliteration was assessed from reports of angiographic brain imaging after
164 intervention. We gave precedence to obliteration confirmed by catheter angiography, otherwise
165 we relied on magnetic resonance angiography.

166

167 **Statistical methods**

168

169 *Baseline characteristics*

170

171 For analyses of clinical covariates, age was a continuous variable, OHS at presentation was
172 dichotomized into 0-1 versus 2-5, and mode of presentation was dichotomized into seizure(s)

173 versus other (although, if following presentation a clinical event occurred which led to
174 intervention, this subsequent event became the mode of presentation in the intervention group).
175 We dichotomized bAVM nidus location into deep (involving the basal ganglia, internal capsule,
176 thalamus, hypothalamus, limbic system, or corpus callosum) versus other. We dichotomized
177 venous drainage into exclusively deep versus other, and bAVM nidus maximum diameter into
178 <3cm versus ≥3cm. We separately derived the bAVM Spetzler-Martin grade, which predicts the
179 likelihood of morbidity from bAVM excision based on bAVM size, venous drainage pattern, and
180 eloquence of surrounding brain (grade 1 lowest risk to grade 5 highest risk).¹⁶

181

182 *Follow-up*

183

184 The primary outcome was the first occurrence of handicap (OHS 2-5, signifying, “some restrictions
185 to lifestyle, but the patient can look after themselves” or worse) sustained for at least two
186 successive years *after* inception (i.e. the baseline OHS rating was not included in the outcome
187 measure) or death (OHS 6) of any cause. The secondary outcome was non-fatal symptomatic
188 stroke (intracranial hemorrhage, cerebral infarction, or focal neurological deficit persisting or
189 progressing for >24 hours) or death due to the bAVM or intervention.

190

191 *Sample size*

192

193 The number of adults diagnosed with unruptured bAVM in our population over ten years
194 determined our sample size, but the timing of our analyses during follow-up was determined by
195 the accumulation of sufficient primary and secondary outcomes to power the multivariable model
196 to include five important covariates without over-fitting.²⁰

197

198 *Analytical methods*

199

200 RA-SS conducted analyses according to a statistical analysis plan approved by the Steering

201 Committee before data extraction (www.saivms.scot.nhs.uk/pdf/resPaper/2013_07_05_SAP.pdf).

202 Completeness of follow-up data was quantified as a proportion of all the potential follow-up time

203 that could have been accrued prior to death or the last available follow-up.²¹ Survival analyses of

204 time to first event started at inception and stopped at the date of the first outcome or the date of

205 censoring, whichever occurred sooner. For the primary outcome censoring occurred at last

206 available follow-up, before which we disregarded missing OHS scores. For the secondary outcome,

207 censoring occurred at last available follow-up or death (possibly or definitely not attributable to

208 bAVM). Adults managed conservatively who had a secondary outcome event that led to

209 intervention remained in the conservative management group for outcome analyses.

210

211 Bivariate analyses were performed using life tables and Kaplan-Meier estimates to analyze follow-

212 up data accrued by 12 years (when ~10% of the cohort remained under follow-up²²) with

213 differences between intervention and conservative management determined by the log-rank test

214 and hazard ratio (HR) from Cox regression, with intervention as the referent category. We pre-

215 specified multivariable analyses to adjust HRs when proportional hazards assumptions were

216 satisfied.²³ Covariates were selected from the following list, in the following order which was

217 determined by the clinical relevance and likely completeness of the covariates, until the number of

218 outcomes per covariate would be below ten with the addition of another covariate²⁰: clinical

219 influences on functional outcome ([1] age at inception, [2] mode of clinical presentation,²⁴ and [3]

220 baseline OHS score [for the primary outcome only]) and vascular anatomy that influences either

221 the risk of bAVM hemorrhage ([4] bAVM nidus location and [5] bAVM venous drainage pattern^{1,2})

222 or the risk of intervention ([6] maximum bAVM nidus diameter^{10,16}). Covariates were entered

223 simultaneously into the regression model. In a supplementary analysis, we derived a model to
224 predict the occurrence of intervention (using age at presentation, receipt of a catheter angiogram,
225 and sex) and adjusted the multivariable models of the primary and secondary outcomes for these
226 propensity scores.

227

228 RA-SS used IBM SPSS Statistics (version 19.0), Stata (version 11.2), StatsDirect (version 2.7.8), and
229 Confidence Interval Analysis software to calculate: parametric statistics for between-group
230 comparisons when continuous data obeyed a normal distribution and non-parametric statistics
231 when they did not; exact tests in the analysis of categorical data; and HRs with Cox regression
232 analyses. All reported P values are two-sided ($\alpha=0.05$).

233

234 **RESULTS**

235

236 **Baseline characteristics**

237

238 During 1999-2003 and 2006-2010, 213 adults were newly diagnosed with at least one definite
239 unruptured bAVM, of whom 204 were eligible for analysis (Figure 1). 103 underwent intervention.
240 101 underwent conservative management (five of whom had a bleed during follow-up and
241 subsequently underwent intervention). Adults receiving intervention were younger, more likely to
242 present with seizure(s), more likely to have a catheter angiogram and less likely to have a
243 maximum bAVM diameter >6cm (Table 1).

244

245

246

247

248 **Conservative management**

249

250 101 adults were managed conservatively, which involved usual care (e.g. pharmacological
251 treatment of seizures) but no intervention. In this group, embolization was attempted but did not
252 proceed in two adults (because of spontaneous bAVM obliteration 12 days after presentation in
253 one adult and the demonstration of unsuitable vascular anatomy on superselective angiography in
254 another) and three adults underwent intervention for a remote intracranial aneurysm, but the
255 bAVM was not treated. A second bAVM spontaneously obliterated 2·4 years after presentation.

256

257 **Intervention**

258

259 103 adults received their first intervention after median 13 months (inter-quartile range [IQR] 7-
260 19, range 0-97) following presentation (eFigure 1). Embolization was attempted but did not
261 proceed because of unsuitable vascular anatomy in four adults (subsequently embolization was
262 possible in one and three underwent stereotactic radiosurgery). Two-thirds received single-
263 modality intervention and one-third received multi-modality intervention over median 12 months
264 (eFigure 2 and eTable 1). 83 adults had catheter angiography and 14 had magnetic resonance
265 angiography following their last intervention, demonstrating bAVM obliteration in 63% after
266 single-modality and 71% following multi-modality intervention (eTable 1). Adults undergoing
267 stereotactic radiosurgery had their most recent imaging study after mean 32±15 months following
268 their most recent intervention.

269

270

271

272

273 **Outcome after intervention or conservative management**

274

275 We followed 204 adults with bAVM who were alive at presentation for a median of 6·9 years (IQR
276 4·0-11·0) and a total of 1,479 person-years (of 1,567 potential person-years; overall completeness
277 94%²¹). The median duration of follow-up was longer after intervention (9·4 years, IQR 5·0-11·9)
278 than during conservative management (5·2 years, IQR 3·0-9·7; $p=0\cdot002$) because three-quarters of
279 the 41 deaths occurred during conservative management (Figure 1 and eFigure 3 and eFigure 4).

280

281 For the primary outcome, the proportional hazards assumption was met over the first four years
282 of follow-up. During this time the rate of progression to the primary outcome was lower during
283 conservative management than after intervention (36 vs. 39 events, 9·5 vs 9·8 per 100 person
284 years, adjusted HR 0·59, 95% confidence interval [CI] 0·35-0·99; Table 2 and Figure 2), but rates
285 were not different when subsequent time periods were analysed separately (4-8 years, 8 vs. 8
286 events, adjusted HR 1·07, 95% CI 0·37-3·16; 8-12 years, 5 vs. 1 event, adjusted HR 4·70, 95% CI
287 0·29-77·42). Over 12 years, the death rate was higher during conservative management than after
288 intervention (31 vs. 10 events, 3·7 vs 1·1 per 100 person years, HR 3·64, 95% CI 1·78-7·43; eFigure
289 3). This was unrelated to bAVM or intervention (log-rank $p=0\cdot29$) but attributable to deaths from
290 other causes (log-rank $p<0\cdot001$); these differences disappeared after age-adjustment (eTable 2).

291

292 For the secondary outcome, the proportional hazards assumption was met over 12 years of
293 follow-up, during which time the rate of progression to the secondary outcome was lower during
294 conservative management than after intervention (14 vs. 38 events, 1·6 vs 3·3 per 100 person
295 years, adjusted HR 0·37, 95% CI 0·19-0·72; Table 2 and Figure 3), largely because of symptomatic
296 strokes due to intervention (Figure 1), 7 of which occurred within 30 days of first intervention.

297 After these first events, there were 12 more secondary outcomes in the intervention group, and
298 one during conservative management.

299

300 **Sensitivity and supplementary analyses**

301

302 In pre-specified sensitivity analyses, the association of conservative management with the primary
303 outcome remained the same over four years after removing adults who experienced outcomes
304 before bAVM intervention (34 vs. 39 events, 9.0 vs 9.8 per 100 person years, adjusted HR 0.58,
305 95% CI 0.34-0.99) or when the two adults who had intervention attempted but not given were re-
306 allocated to the intervention group (34 vs. 41 events, 9.3 vs 10.0 per 100 person years, adjusted
307 HR 0.53, 95% CI 0.32-0.90). The association with the secondary outcome was similar whether
308 including pre-intervention clinical course in the conservative management group (18 vs. 39 events,
309 2.1 vs 3.4 per 100 person years, unadjusted HR 0.27, 95% CI 0.16-0.47), including pre-intervention
310 clinical course in the intervention group (14 vs. 33 events, 1.5 vs 2.8 per 100 person years,
311 adjusted HR 0.50, 95% CI 0.25-0.98),²⁵ including secondary outcomes that were possibly due to the
312 bAVM (18 vs. 39 events, 2.1 vs 3.3 per 100 person years, adjusted HR 0.43, 95% CI 0.23-0.78), or
313 reallocating the two adults who had intervention attempted but not given to the intervention
314 group (14 vs. 38 events, 1.6 vs 3.2 per 100 person years, adjusted HR 0.42, 95% CI 0.22-0.79).

315

316 We pre-specified a supplementary analysis of ARUBA's primary outcome (the composite event of
317 death from any cause or symptomatic stroke). However, the proportional hazards assumption was
318 violated (eFigure 5) precluding multivariable analysis, because of the excess of deaths of any cause
319 in the conservative management group in our study (Figure 1 and eFigure 3).

320

321 A post hoc analysis restricted to adults who were OHS 0-1 at baseline did not change the
322 association between conservative management and the primary outcome (12 vs. 24 events, 5.5 vs
323 9.0 per 100 person years, adjusted HR 0.42, 95% CI 0.20-0.89 over four years) or secondary
324 outcome (7 vs. 20 events, 1.3 vs 2.5 per 100 person years, adjusted HR 0.35, 95% CI 0.14-0.87).

325

326 In post hoc analyses, we found differences between the two cohort epochs in some covariates.
327 Therefore, we added a cohort epoch term to our multivariable models, which had sufficient
328 outcomes to allow the addition of another covariate. The strength and statistical significance of
329 the associations in our multivariable analyses of the primary and secondary outcomes (Table 2) did
330 not change, but the 2006-2010 cohort was associated with faster progression to the secondary
331 outcome (27 vs. 25 events, 4.6 vs 1.8 per 100 person years, adjusted HR 2.37, 95% CI 1.28-4.36).
332 Post hoc multivariable analyses also adjusted for scores modelled on propensity to intervention
333 did not change the association between conservative management and the primary outcome (36
334 vs. 39 events, 9.5 vs 9.8 per 100 person years, adjusted HR 0.50, 95% CI 0.27-0.94; eTable 3) or
335 secondary outcome (14 vs. 38 events, 1.6 vs 3.3 per 100 person years, adjusted HR 0.39, 95% CI
336 0.20-0.74; eTable 4).

337

338 **DISCUSSION**

339

340 In a prospective, population-based inception cohort study of adults with unruptured bAVM, we
341 found that conservative management was associated with a lower rate of progression to sustained
342 handicap or death of any cause over four years, and a lower risk of bAVM-related symptomatic
343 stroke or death over 12 years, having adjusted for baseline imbalances and performed several
344 sensitivity analyses.

345

346 One randomized controlled trial comparing conservative management with intervention for
347 unruptured bAVMs (ARUBA) was published recently.^{8,9} Non-randomized observational studies and
348 randomized trials sometimes concur,^{26,27} and in this case the similarities support the
349 generalizability of the results: treated participants were similar in age, sex, incidental mode of
350 presentation, lobar bAVM nidus location, superficial venous drainage pattern, and Spetzler-Martin
351 grades (Table 1), and they received multi-modality intervention with the same frequency (eTable
352 1).⁹ Furthermore, the association between conservative management and stroke or death related
353 to bAVM or its intervention over 12 years in this observational study (adjusted HR 0·37, 95% CI
354 0·19-0·72) was similar to the effect of conservative management on stroke or death of any cause
355 over six years in the ARUBA as-randomized analysis (HR 0·27, 95% CI 0·14-0·54).⁹ The similarity of
356 the results of this observational study and ARUBA and the persistent difference between the
357 outcome of conservative management and intervention during 12-year follow-up in our study
358 support the superiority of conservative management to intervention for unruptured bAVMs,
359 which may deter these patients and physicians from intervention.

360

361 The strengths of this study include: thorough case ascertainment¹⁵; a population-based sampling
362 frame to maximize external validity; a concurrent control group; sufficient time to allow the
363 effects of multi-modality intervention and stereotactic radiosurgery to be complete by the end of
364 follow-up; internal validity from using independent imaging review and outcome assessment with
365 reference to published criteria; minimisation of bias by using outcomes that were rated and
366 adjudicated independently of the doctors caring for these adults in clinical practice; and 94%
367 completeness of the entire duration of follow-up for all adults. The clinical outcome and
368 proportions of bAVM obliterated by intervention in Scotland appear generalizable, by being at
369 least as good as reports in systematic reviews⁶ and the USA Nationwide Inpatient Sample

370 database.²⁸ Furthermore, the rate of hemorrhage from unruptured bAVMs (18%, 95% CI 11-30
371 after 12 years; Figure 3) was consistent with reported rates.^{1,2}

372

373 This study also has several limitations. Our comparison of intervention and conservative
374 management was not randomized, so selection bias led to adults undergoing intervention being
375 younger, presenting more often with seizure(s), and having smaller AVM nidus diameters (Table
376 1). Confounding by indication may affect our results, but the bAVM intervention group appeared
377 to have favourable prognostic factors, and adjustment for propensity to intervention did not
378 change our findings. Both the robustness of our findings in sensitivity analyses, as well as
379 consistency between our findings and ARUBA⁹ are reassuring. The primary outcome did not
380 include the baseline measurement of handicap (and therefore allowed recovery from initial
381 presentation) and crucially it allowed for recovery from the known early complications after
382 intervention by requiring handicap to be sustained for at least two successive years. The primary
383 outcome was difficult to interpret beyond four years, because of the high frequency of bAVM-
384 unrelated deaths in the conservative management group, which was attributable to the imbalance
385 in age between the groups at baseline. Long-term follow-up in both this study as well as the
386 ARUBA trial is needed to establish whether the superiority of conservative management will
387 persist or change.

388

389 **Conclusions**

390 Among adults diagnosed with unruptured bAVM, the use of conservative management compared
391 with intervention was associated with better clinical outcomes over 4 years. However, longer
392 follow-up is required to understand whether this association is persistent.

393 **CONTRIBUTORS**

394

395 RA-SS and CPW designed the study, supported by the SAIVMs Steering Committee. RA-SS, JvB, CBJ,
396 TW, CJW, and ZS collected data. RJS, JdP, and PMW assessed brain imaging. RA-SS checked,
397 analysed and interpreted the data according to a statistical analysis plan developed and approved
398 by the SAIVMs Steering Committee. RA-SS drafted the paper, and all co-authors reviewed the final
399 version.

400

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486 **CONFLICTS OF INTEREST**

487

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489 All other authors have nothing to disclose.

490

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FIGURE LEGENDS

FIGURE 1 – Flowchart of included participants.

bAVM = arteriovenous malformation

* Oxford Handicap Scale scores were not available for three patients. [†] Five patients experiencing bAVM hemorrhage during conservative management subsequently had intervention, but remained in the conservative management group for analysis of the primary outcome

FIGURE 2 – Progression to the primary outcome (first occurrence after inception of death of any cause or handicap [Oxford Handicap Scale Score 2-5] sustained for two or more successive years) during 12 years of prospective follow-up.

Error bars represent the 95% confidence intervals of the cumulative proportions at four and 12 years after inception.

FIGURE 3 – Progression to the secondary outcome (first occurrence after inception of a non-fatal intracranial hemorrhage, cerebral infarct, or persistent/progressive non-hemorrhagic focal neurological deficit, or death, due to a brain arteriovenous malformation [bAVM] or intervention complication) during 12 years of prospective follow-up.

Error bars represent the 95% confidence intervals of the cumulative proportions at four and 12 years after inception.

TABLE 1 – Baseline characteristics of adults with a definite diagnosis of an unruptured brain arteriovenous malformation (bAVM).

	Conservative management		Intervention		Significance (p value)
	(n=101)		(n=103)		
Age at inception (mean \pm SD), years	53	\pm 16	41	\pm 13	<0.001
Female	39	(39%)	44	(43%)	0.551
Mode of presentation					0.009
Incidental	61	(60%)	40	(39%)	
Seizure(s)	33	(33%)	52	(50%)	
First seizure	15		26		
Epilepsy	18		26		
Focal neurological deficit	7	(7%)	11	(11%)	
Presentation Oxford Handicap Scale 0-1	61	(60%)	69	(67%)	0.097
bAVM nidus location					0.404
Brainstem	3	(3%)	1	(1%)	
Cerebellum	1	(1%)	2	(2%)	
Deep	3	(3%)	7	(7%)	
Lobar	94	(93%)	93	(90%)	
Eloquent bAVM nidus location	50	(50%)	54	(52%)	0.676
Maximum bAVM nidus diameter (n=182)					0.012
<3cm	45	(51%)	50	(54%)	
3-6cm	36	(40%)	43	(46%)	
>6cm	8	(9%)	0	(0%)	
Catheter angiogram done	46	(46%)	96	(93%)	<0.001
Venous drainage pattern (n=142)					0.618
Superficial	30	(65%)	69	(72%)	
Both deep and superficial	13	(28%)	20	(21%)	
Exclusively deep	3	(7%)	7	(7%)	
Spetzler-Martin Grade¹⁶ (n=142)					0.212
I	9	(20%)	21	(22%)	
II	15	(33%)	36	(38%)	
III	12	(26%)	29	(30%)	
IV	8	(17%)	10	(10%)	
V	2	(4%)	0	(0%)	
Co-existing intracranial aneurysms					0.236
Associated only	20	(20%)	19	(18%)	
Remote and associated	1	(1%)	6	(6%)	
Remote only	4	(4%)	2	(2%)	

TABLE 2 – Bivariate and multivariable Cox proportional hazards analyses of the first occurrence of a primary or secondary outcome.

	Primary outcome [¶]				Secondary outcome [‡]			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)		Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)	
			Unadjusted bivariate	Multivariable adjusted*			Unadjusted bivariate	Multivariable adjusted [§]
Treatment								
Conservative management	98	36			101	14		
Intervention (referent)	103	39	0.82 (0.52-1.29)	0.59 (0.35-0.99)	103	38	0.31 (0.17-0.58)	0.37 (0.19-0.72)
Age at inception (per year increase)	201	75	1.01 (0.99-1.03)	1.01 (0.99-1.03)	204	52	0.98 (0.96-0.99)	0.99 (0.97-1.01)
Presentation								
Seizure(s)	85	33			85	26		
Other (referent)	116	42	1.04 (0.66-1.65)	0.74 (0.43-1.29)	119	26	1.42 (0.82-2.44)	1.21 (0.68-2.16)
Presentation OHS								
2-5	74	39			-	-		
0-1 (referent)	127	36	2.23 (1.41-3.50)	2.48 (1.49-4.12)	-	-	-	-
bAVM location								
Deep	10	3			10	5		
Other (referent)	191	72	0.75 (0.24-2.39)	0.73 (0.23-2.39)	194	47	1.99 (0.79-5.01)	1.71 (0.66-4.46)

[¶] first occurrence during four years of follow-up after inception of death or handicap [Oxford Handicap Scale Score (OHS) 2-5] sustained for two or more successive years; [‡] first occurrence during 12 years of follow-up after inception of a non-fatal intracranial hemorrhage, cerebral infarct, or persistent / progressive non-hemorrhagic focal neurological deficit, or death, due to a brain arteriovenous malformation [bAVM] or intervention complication; * adjusted for intervention, age at inception, mode of presentation, bAVM location, and OHS at presentation; [§] adjusted for intervention, age at inception, mode of presentation, and bAVM location

FIGURE 1 – Flowchart of included participants.

bAVM = arteriovenous malformation

* Oxford Handicap Scale scores were not available for three patients. [¶] Five patients experiencing bAVM hemorrhage during conservative management subsequently had intervention, but remained in the conservative management group for analysis of the primary outcome

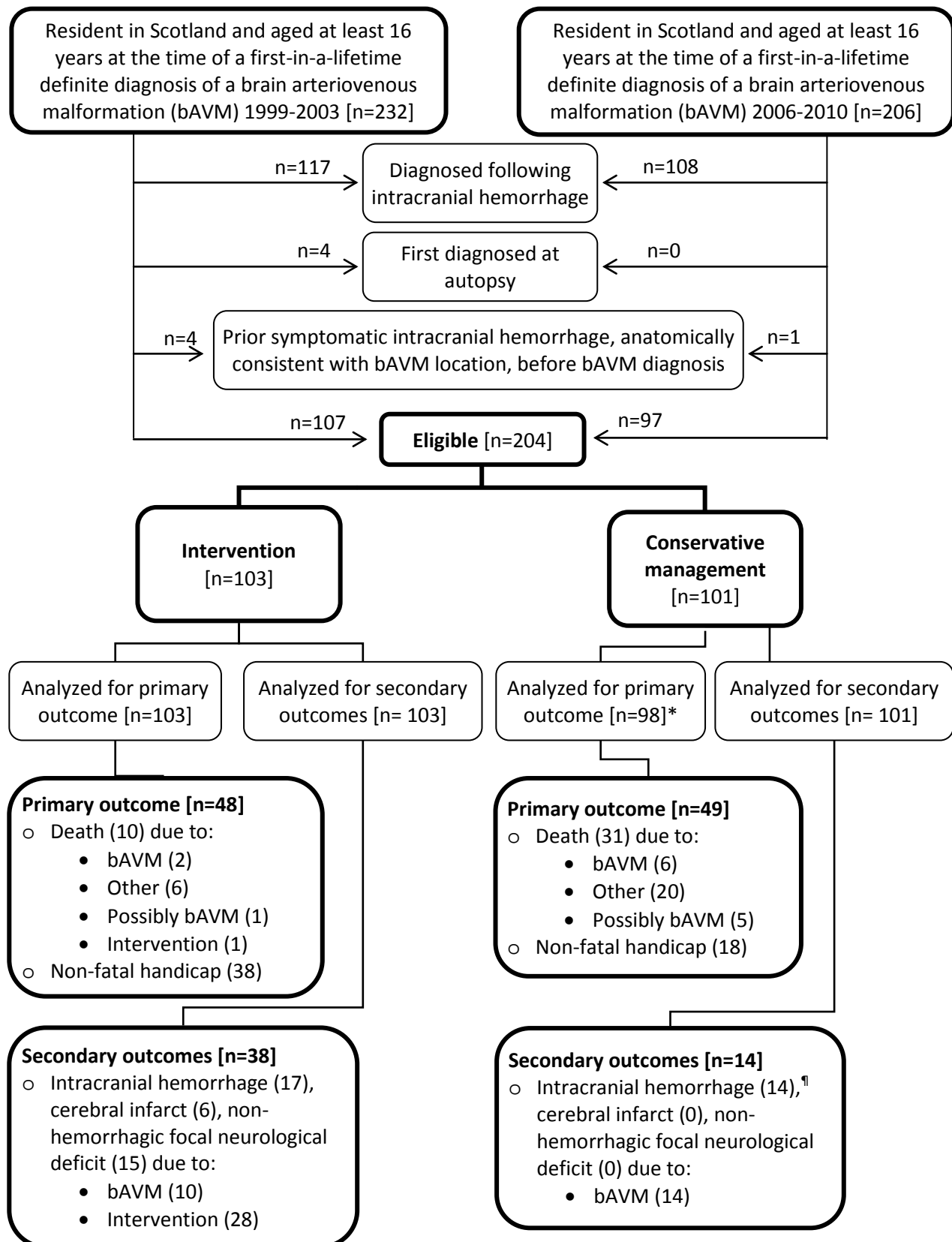


FIGURE 2 – Progression to the primary outcome (first occurrence after inception of death of any cause or handicap [Oxford Handicap Scale Score 2-5] sustained for two or more successive years) during 12 years of prospective follow-up.

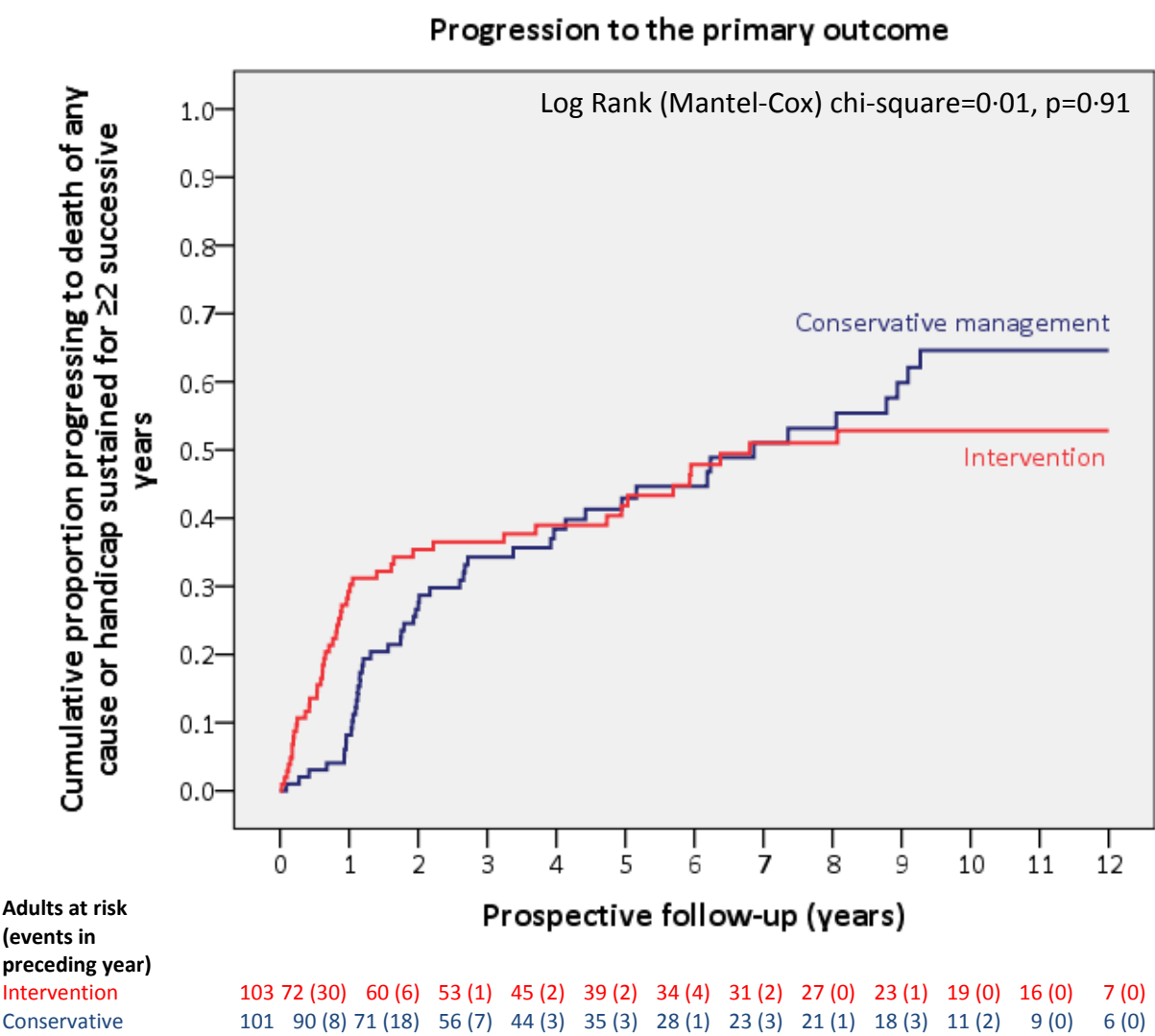
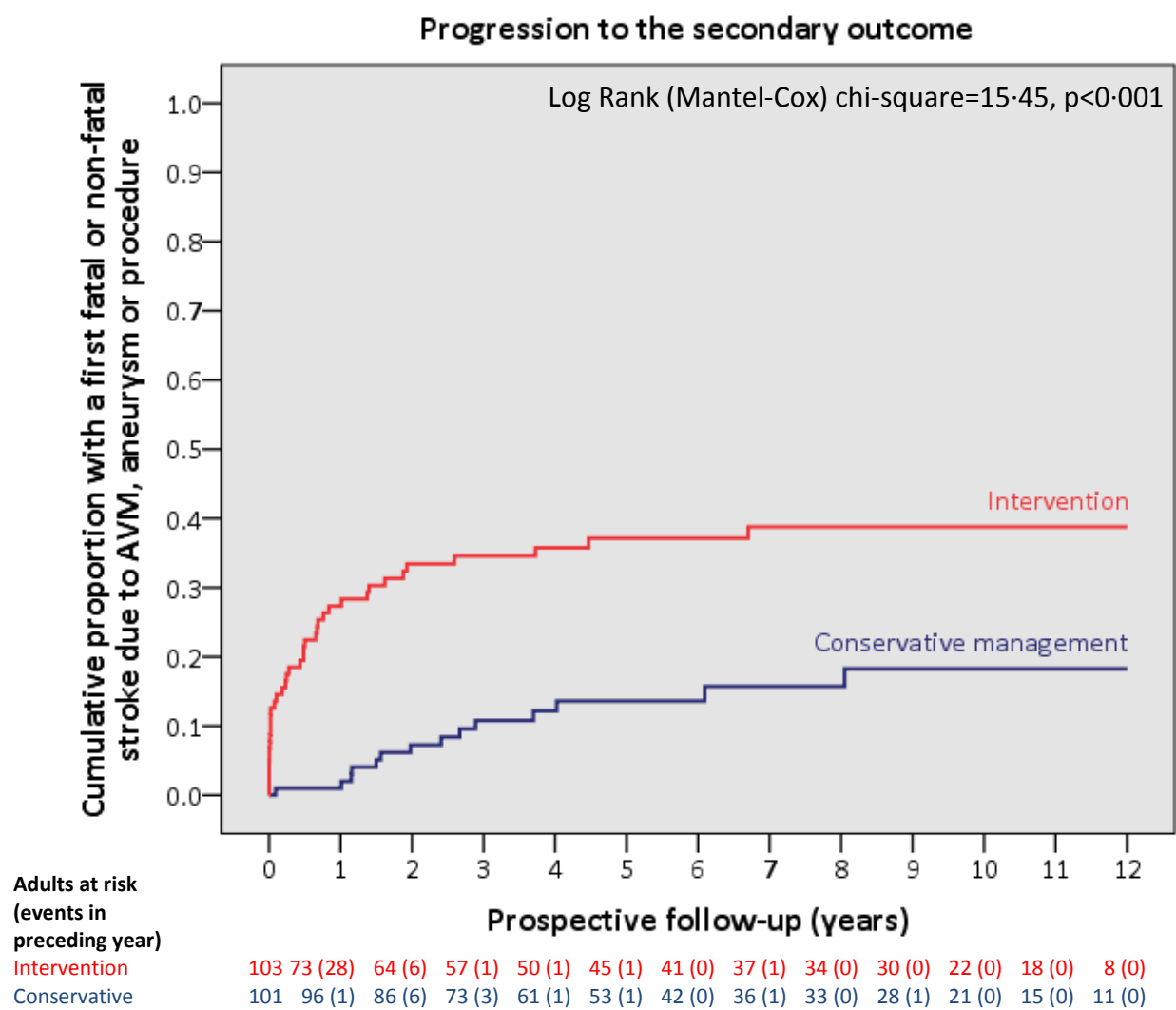


FIGURE 3 – Progression to the secondary outcome (first occurrence after inception of a non-fatal intracranial hemorrhage, cerebral infarct, or persistent/progressive non-hemorrhagic focal neurological deficit, or death, due to a brain arteriovenous malformation [bAVM] or intervention complication) during 12 years of prospective follow-up.



ONLINE-ONLY SUPPLEMENT

eFIGURE 1 – Time to first intervention for an unruptured brain arteriovenous malformation or associated arterial aneurysm after initial presentation among the 103 adults in the intervention group

eFIGURE 2 – Time between first and last intervention for an unruptured brain arteriovenous malformation or associated arterial aneurysm among the 103 adults in the intervention group

eTABLE 1 – Type of intervention and extent of angiographic obliteration among the 103 adults in the intervention group

eFIGURE 3 – Progression to death of any cause among the 204 adults with unruptured bAVM during 12 years of prospective follow-up

eTABLE 2 – Bivariate and multivariable Cox proportional hazards analyses of the first occurrence of death of any cause among the 204 adults with unruptured bAVM during 12 years of prospective follow-up

eFIGURE 4 – Stacked bar chart of the proportions of the 204 adults with unruptured bAVM who were followed-up in each year on the Oxford Handicap Scale, stratified by treatment group for comparison

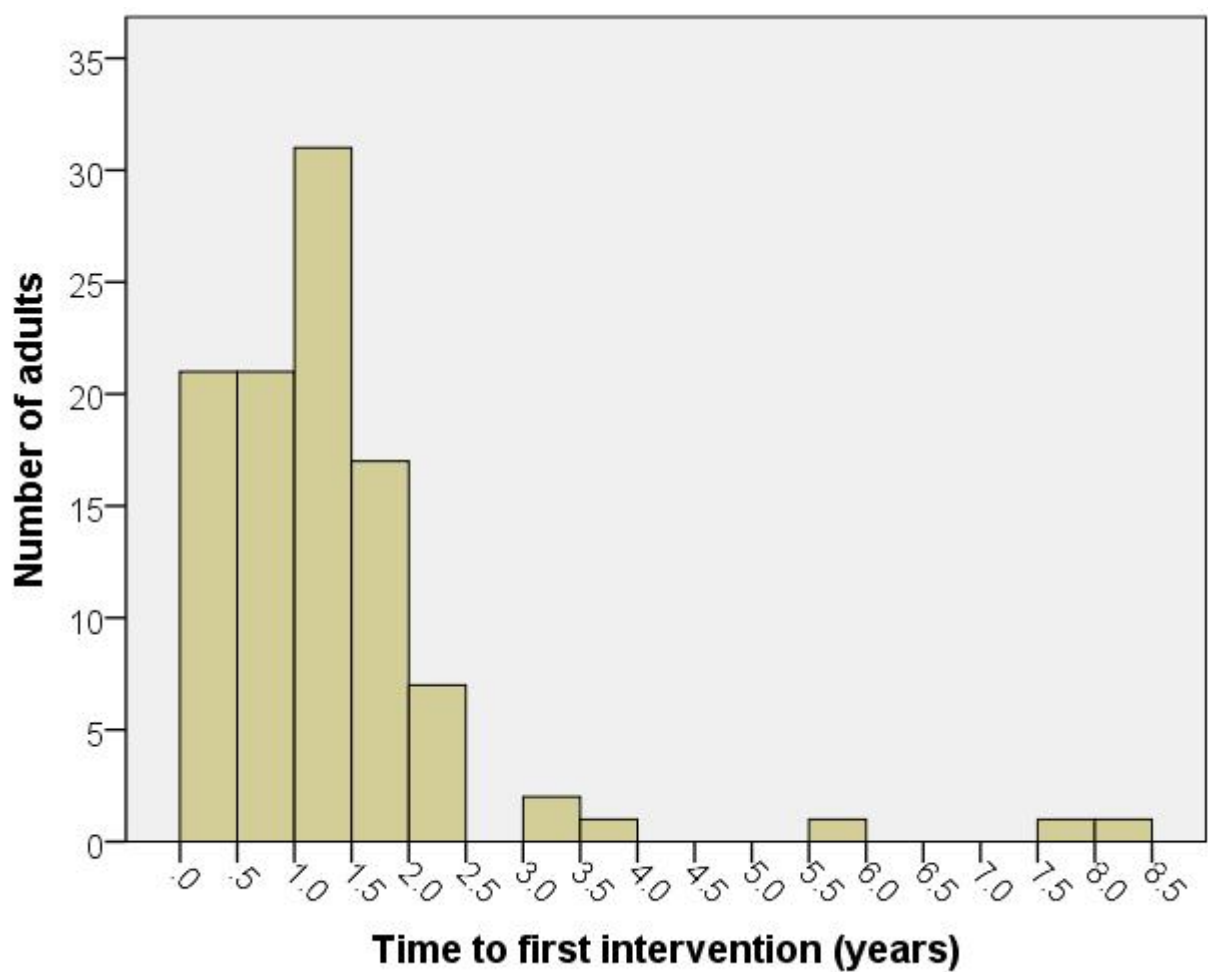
eFIGURE 5 – Progression to death from any cause or symptomatic stroke among the 204 adults with unruptured bAVM during 12 years of prospective follow-up

eTABLE 3 – Multivariable Cox proportional hazards analysis of the first occurrence of the primary outcome during four years of follow-up among the 204 adults with unruptured bAVM, adjusted for propensity score

eTABLE 4 – Multivariable Cox proportional hazards analysis of the first occurrence of the secondary outcome during 12 years of follow-up among the 204 adults with unruptured bAVM, adjusted for propensity score

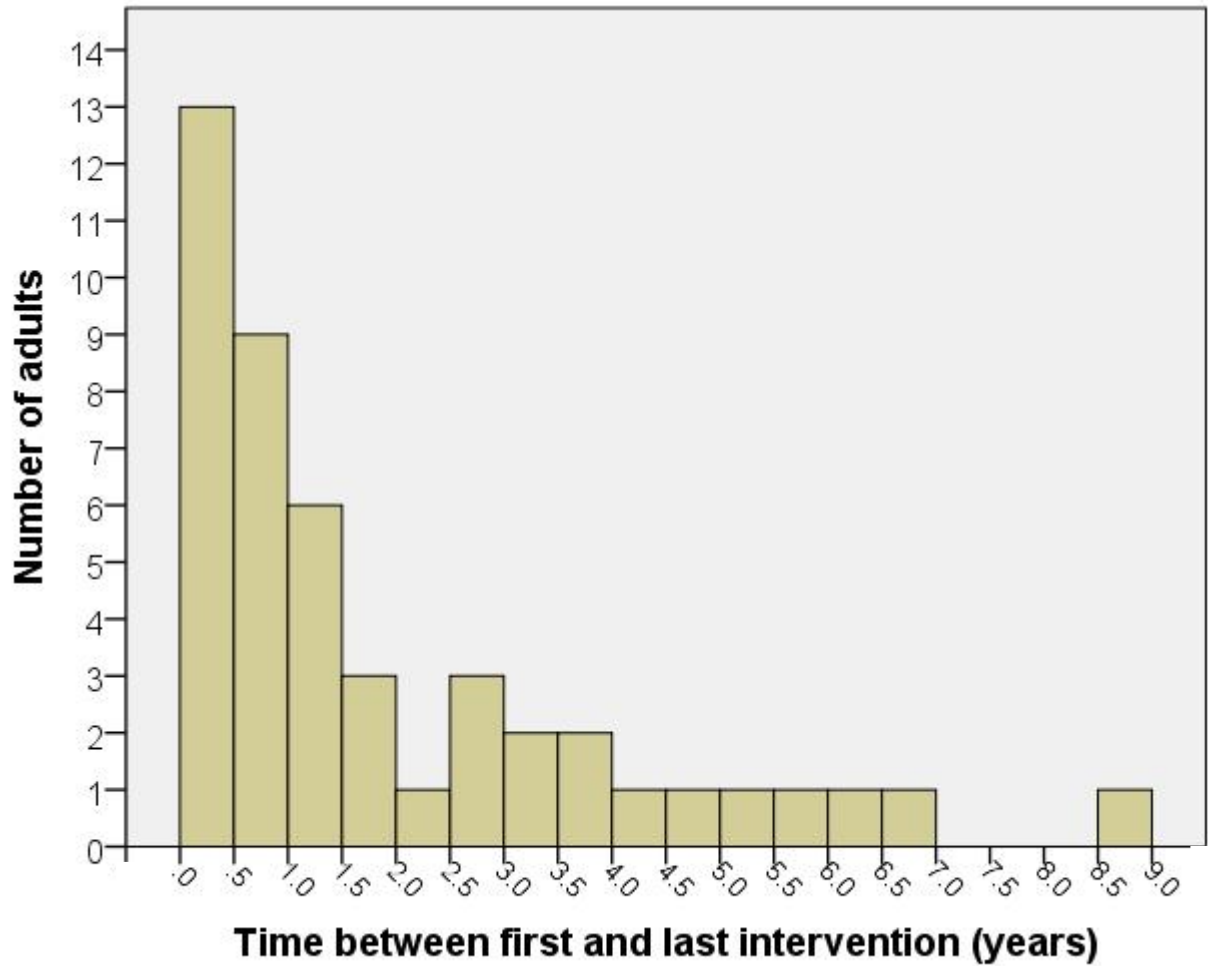
eFIGURE 1 – Time to first intervention for an unruptured brain arteriovenous malformation or associated arterial aneurysm after initial presentation among the 103 adults in the intervention group.

Each bin includes values greater than or equal to the lower limit and less than the upper limit.



eFIGURE 2 – Time between first and last intervention for an unruptured brain arteriovenous malformation or associated arterial aneurysm among the 103 adults in the intervention group.

Each bin includes values greater than or equal to the lower limit and less than the upper limit.

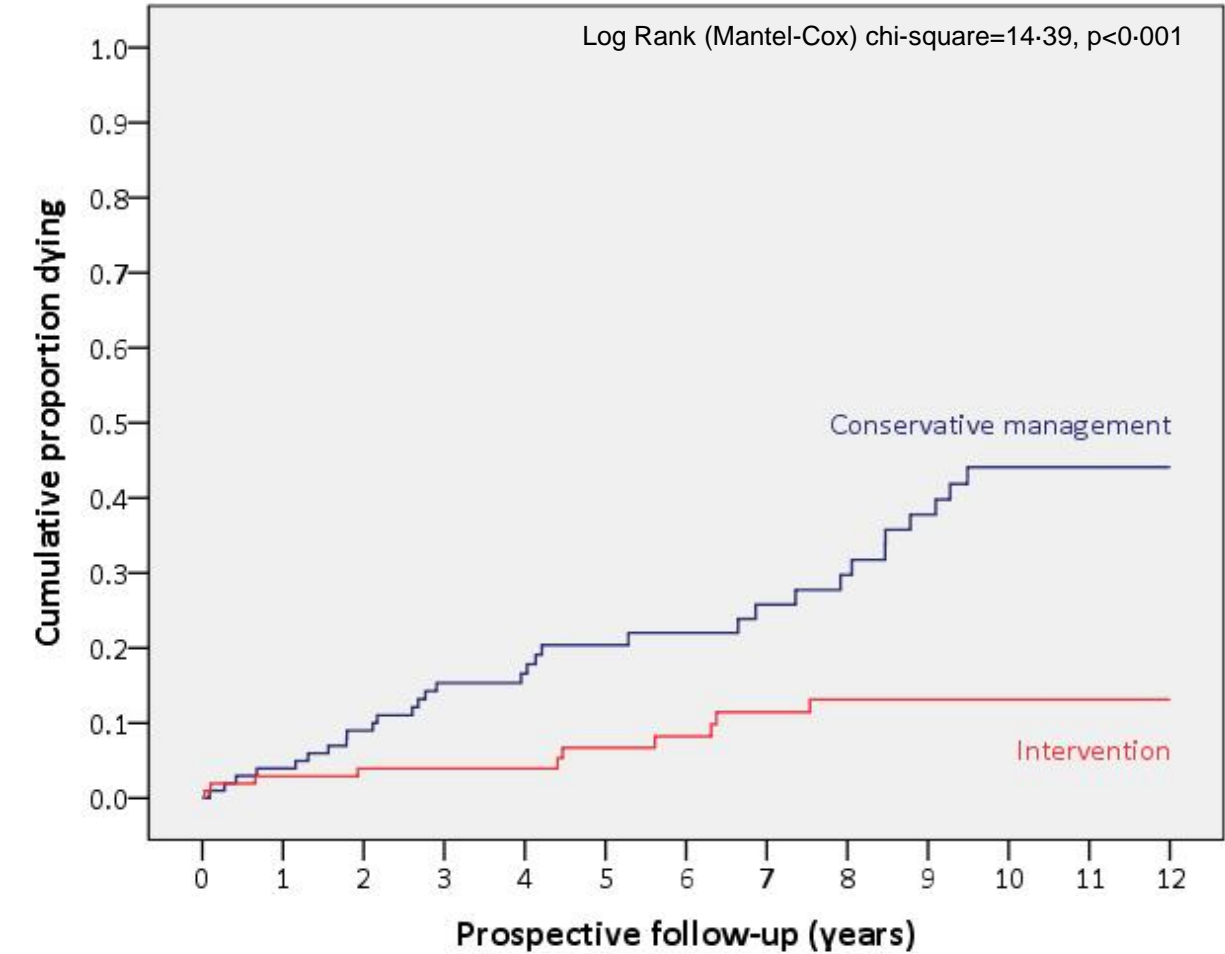


eTABLE 1 – Type of intervention and extent of angiographic obliteration among the 103 adults in the intervention group.

Intervention	n	Completely obliterated		Partially obliterated		No follow-up imaging	
Single modality							
Stereotactic radiosurgery	28	18	(64%)	8	(29%)	2	(7%)
Endovascular embolisation	22	10	(45%)	10	(45%)	2	(10%)
Microsurgical excision	18	15	(83%)	1	(6%)	2	(11%)
Sub-total	68	43	(63%)	19	(28%)	6	(9%)
Multimodality **							
Endovascular embolisation and stereotactic radiosurgery	20	11	(55%)	9	(45%)	0	(0%)
Endovascular embolisation and microsurgical excision	12	12	(100%)	0	(0%)	0	(0%)
Stereotactic radiosurgery and microsurgical excision	2	2	(100%)	0	(0%)	0	(0%)
Endovascular embolisation, microsurgical excision, and stereotactic radiosurgery	1	0	(0%)	1	(100%)	0	(0%)
Sub-total	35	25	(71%)	10	(29%)	0	(0%)

** p<0.01 comparing the proportion completely obliterated in four multimodality approaches

eFIGURE 3 – Progression to death of any cause among the 204 adults with unruptured bAVM during 12 years of prospective follow-up.



Adults at risk (events in preceding year)													
Conservative	101	96 (4)	90 (5)	78 (6)	66 (1)	57 (3)	45 (1)	39 (2)	35 (2)	31 (4)	24 (3)	15 (0)	11 (0)
Intervention	103	99 (3)	94 (1)	82 (0)	72 (0)	63 (2)	59 (1)	53 (2)	50 (1)	43 (0)	32 (0)	26 (0)	12 (0)

eTABLE 2 – Bivariate and multivariable Cox proportional hazards analyses of the first occurrence of death of any cause among the 204 adults with unruptured bAVM during 12 years of prospective follow-up.

	Death of any cause			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)	
			Unadjusted bivariate	Multivariable adjusted*
Treatment				
Conservative management	101	31	3.64 (1.78-7.43)	1.62 (0.72-3.65)
Intervention (referent)	103	10		
Age at inception (per year increase)	204	41	1.07 (1.04-1.09)	1.04 (1.02-1.07)
Presentation				
Seizure(s)	85	11	0.41 (0.21-0.82)	0.45 (0.20-0.98)
Other (referent)	119	30		
Presentation OHS				
2-5	74	23	3.30 (1.76-6.16)	3.50 (1.77-6.89)
0-1 (referent)	130	18		

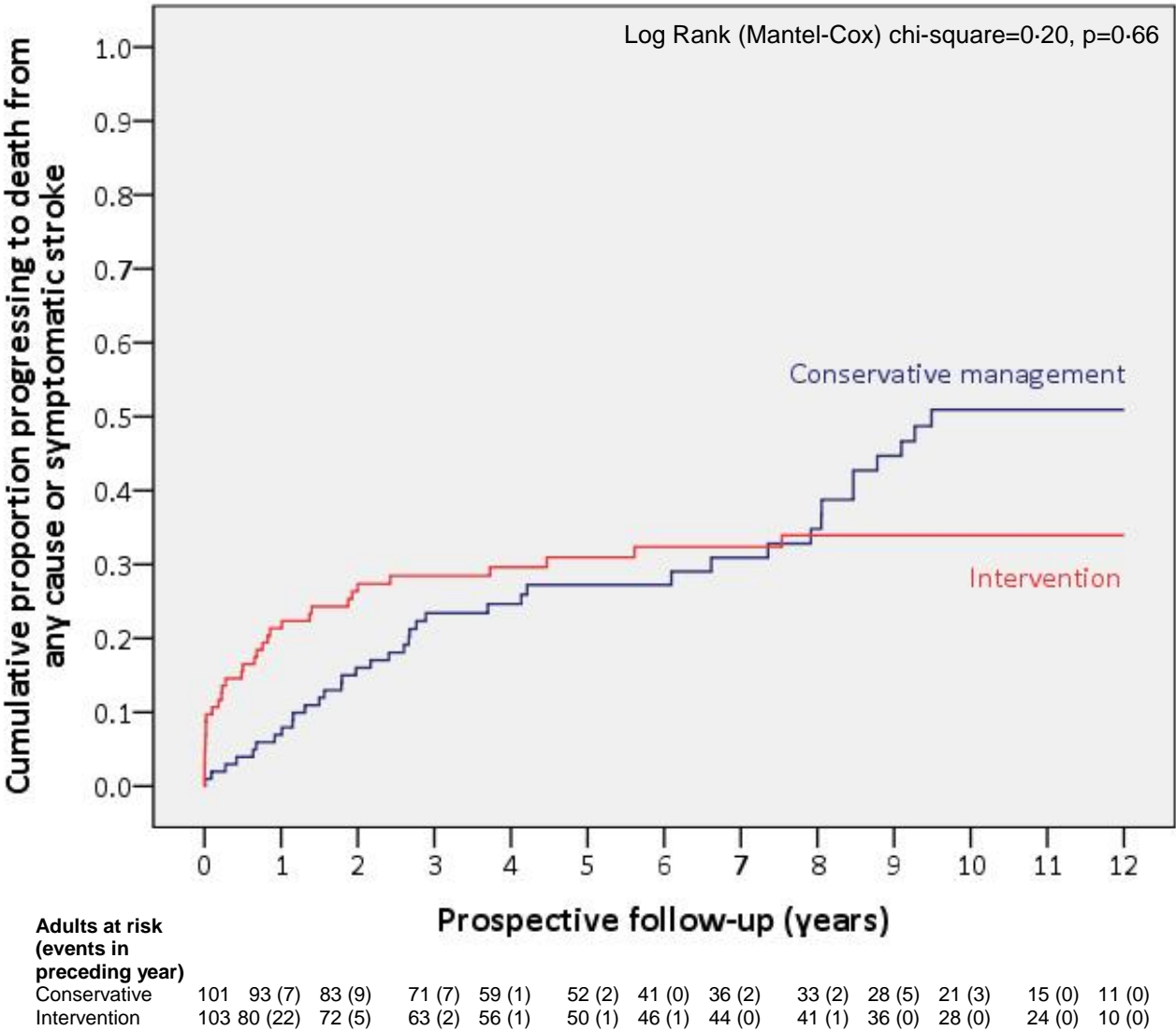
* adjusted for intervention, age at inception, mode of presentation, and OHS at presentation

eFIGURE 4 – Stacked bar chart of the proportions of the 204 adults with unruptured bAVM who were followed-up in each year on the Oxford Handicap Scale, stratified by treatment group for comparison.

Deaths are illustrated cumulatively so the annual case fatality rate is over-estimated.



eFIGURE 5 – Progression to death from any cause or symptomatic stroke among the 204 adults with unruptured bAVM during 12 years of prospective follow-up.



eTABLE 3 – Multivariable Cox proportional hazards analysis of the first occurrence of the primary outcome during four years of follow-up among the 204 adults with unruptured bAVM, adjusted for propensity score.

Primary outcome (over four years), adjusted for propensity score			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)
			Multivariable adjusted
Treatment			
Conservative management	98	36	0.50 (0.27-0.94)
Intervention (referent)	103	39	
Age (per year increase)	201	75	1.01 (0.99-1.03)
Presentation			
Seizure(s)	85	33	0.69 (0.39-1.23)
Other (referent)	116	42	
bAVM location			
Deep	10	3	0.73 (0.22-2.41)
Other (referent)	191	72	
Presentation OHS			
2-5	74	39	2.48 (1.47-4.19)
0-1 (referent)	127	36	

eTABLE 4 – Multivariable Cox proportional hazards analysis of the first occurrence of the secondary outcome during 12 years of follow-up among the 204 adults with unruptured bAVM, adjusted for propensity score.

Secondary outcome (over 12 years), adjusted for propensity score			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)
			Multivariable adjusted
Treatment			
Conservative management	101	14	0.39 (0.20-0.74)
Intervention (referent)	103	38	
Age (per year increase)	204	52	0.99 (0.97-1.01)
Presentation			
Seizure(s)	85	26	1.15 (0.65-2.04)
Other (referent)	119	26	
bAVM location			
Deep	10	5	1.69 (0.65-2.04)
Other (referent)	194	47	